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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/066,390	PADGETT ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-72,78-83,85 and 87-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-72,78-83,85 and 87-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants are herewith notified that this application has been assigned to the current examiner because Examiner Jeffrey Fredman left the art unit.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2007 has been entered.

3. Claims 66-72, 78-83, 85 and 87-90 were previously pending. Applicants amended claims 66-68, 71, 72, 78-83 and added new claims 91-105. Claims 66-72, 78-83, 85 and 87-105 are pending and will be examined.

4. Applicants' amendments and arguments overcame the following rejections: rejection of claims 66-72, 78-83, 85 and 87-90 under 35 U.S.C. 112, first paragraph, written description; rejection of claims 66-72, 78-83, 85 and 87-90 under 35 U.S.C. 112, second paragraph; rejection of claim 80 under 35 U.S.C. 103(a) over Vind and Arnold; rejection of claims 78 and 79 under 35 U.S.C. 103(a) over Vind and Birkenkamp et al. and rejection of claims 66-74, 81-82, 85 and 87-90 under 35 U.S.C. 103(a) over Vind and Oleykowski et al. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

5. The declaration under 37 CFR 1.132 filed October 30, 2007 is insufficient to overcome the rejection of claims 67, 69-72, 85 and 87-90 under 35 U.S.C. 102(e) based upon Vind as set forth in the last Office action for reasons discussed in the "Response to Arguments" below.

6. This office action contains new grounds for rejection.

Response to Arguments

7. Applicant's arguments filed October 30, 2007 have been fully considered but they are not persuasive.

Regarding the rejection of claims 67, 69-72, 85 and 87-90 under 35 U.S.C. 102(e) as anticipated by Vind, Applicants argue that:

i) Vind does not teach "mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatched nucleotides, e.g., CELI, which is not taught by Vind and which is not a part of normal DNA repair system, in which the endonucleases cleave somewhere upstream or downstream from the mismatch.

ii) The declaration of Dr. Padgett clarifies that the DNA repair system is equivalent to a negative control, or background, and that the reassorted molecules of the instant invention are very different from the output molecules one of ordinary skill in the art would expect to obtain after treatment of a heteroduplex with a DNA repair system.

Regarding i), Applicants did not define what it means for the endonuclease to cut "at the mismatched nucleotide", therefore any distance from the cut is considered to anticipate this term. Further, in claims 67-72, 78-80, 83, 85 and 87-90 no specific endonucleases are required.

Regarding ii), Dr. Padgett's declaration is directed to the properties of molecules obtained in the process of the invention or to the frequencies of shuffling, none of which are claimed.

The rejection is maintained.

B) Regarding the rejection of claim 68 under 35 U.S.C. 103(a) over Vind, Applicants argue that because Vind teaches the use of a cell extract, Vind cannot suggest alternate orders of addition of components because Vind is adding all of the components simultaneously. There is no question

that Vind exemplifies only the cell extract situation. However, Vind clearly teaches the use of "purified" RCR extract (see column 19, line 21, for example). Vind further teaches the specific enzymes required for the assay (see column 8, lines 17-26, where 6 or 7 specific enzymes are mentioned). Therefore, the issue is whether one of ordinary skill in the art would have been motivated to use purified components and alter the order of addition these components. As noted in the rejection, MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction. Therefore, the only real issue is whether, when Vind teaches "purified" extract, one of ordinary skill would appreciate that the enzymes could be purified individually and added. The Federal Circuit has recently provided a detail explanation of the subsidiary requirement for motivation to combine in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006) noting,

> "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with several years experience, there is no doubt that the ordinary artisan possesses the knowledge and motivation sufficient to purify known enzymes using known purification schemes and add them

in any order. Some of the listed motivations of Dystar, to result in a cleaner, more efficient and more durable assay, would motivate the ordinary practitioner to perform such purification.

The rejection is maintained.

Claim Interpretation

8. Regarding the phrase "consisting essentially of", MPEP 2111 notes "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

9. Applicants did not define the term "cleaves at the mismatched nucleotides", therefore cleavage at any distance from the nucleotide will be considered as anticipating this term.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 67, 69-72, 79, 80, 85 and 87-90 are rejected under 35 U.S.C. 102(b) as being anticipated by Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action) as evidenced as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989).

Regarding claim 67, Arnold et al teach an in vitro method of making linear sequence variants comprising:

a) preparing at least one heteroduplex polynucleotide, the heteroduplex having first and second strands (page 2, lines 32, 33; page 3, lines 1-5; lines 11-33; page 4, lines 1-9; since heteroduplex is a double-stranded nucleic acid, it inherently has first and second strands),

b) combining said heteroduplex polynucleotide with enzymes consisting essentially of an effective amount of a mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatched nucleotides, an enzyme or enzymes with 3' to 5' exonuclease activity and an enzyme or enzymes with polymerase activity (Arnold et al. teach mixing the heteroduplexes with either intact cells or cell extracts containing mismatch-endonuclease activity, an enzyme with 3' to 5' exonuclease activity and enzyme with polymerase activity (page 3, lines 2-5;10; page 4, lines 24-26; page 9, lines 12-33; page 16, lines 22-33; page 17, lines 1-33; page 18, lines 1-3). As evidenced by Lahue et al., E. coli contains a DNA polymerase and a ligase which participate in the repair reactions (page 161, second paragraph), therefore by teaching E. coli cells Arnold et al. inherently teach a polymerase. Further, since the E. coli cells contain a repair system which contain cellular repair system with mismatch endonuclease, Arnold et al. inherently teach mismatch endonuclease. Finally, E. coli cells contain enzymes with 3' to 5' exonuclease activity, for example DNA polymerase PolI.),

c) allowing sufficient time for the percentage of complementarity to increase wherein one or more sequence variants are made, thereby increasing diversity in a population of polynucleotides

(Arnold et al. teach allowing sufficient time to proceed with a repair mechanism and produce variant nucleotides (page 18, lines 6-8), therefore inherently increasing diversity of a population of polynucleotides and producing at least one variant), and

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (page 3, lines 11-25), where resulting nucleic acids are inherently separated and recovered by cloning).

Regarding claim 69, Arnold et al teach concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (page 9, lines 21-22, where the cell extract is added).

Regarding claims 70-72, Arnold et al teach the addition of E. coli DNA ligase in cell extracts (page 9, lines 21-22; page 17, line 33; where the cell extract from E. coli is added, which inherently includes E. coli ligase).

Regarding claims 79 and 80, Arnold et al teach the addition of E. coli DNA polymerase I in cell extracts (page 9, lines 21-22, page 17, line 33; where the cell extract from E. coli is added which inherently includes E. coli DNA polymerase I).

Regarding claim 85, Arnold et al teach that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (page 23, lines 10-32; page 24, lines 1-8).

Regarding claim 87, Arnold et al teach performance of the method to generate a library of different nucleotide sequences (page 23, lines 10-32; page 24, lines 1-8, for example).

Regarding claims 88-89, Arnold et al teach screening for changed properties of the sequence (page 3, lines 4, 5; page 4, lines 27-30; page 6, lines 30-33; page 7, lines 1-5; page 9, lines 30-33; page 18, lines 30; page 19, lines 1-9).

Regarding claim 90, Arnold et al teach 56% homology can be used which would result in at least three non-complementary base pairs that performance of the method will generate at least four sequence variants (page 22, 23, page 24, lines 1-8, for example).

12. Claims 67, 69-72, 85 and 87-90 are rejected under 35 U.S.C. 102(e) as being anticipated by Vind (U.S. Patent 6,783,941; cited in the previous office action) (who receives benefit of priority to 60/256,018, filed December 15, 2000).

Regarding claim 67, Vind teaches an in vitro method of making linear sequence variants (see column 2, lines 47-67),from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs separated by complementary base pairs (see column 2, lines 47-67, column 4, lines 16-21 and column 7, lines 15-20, where only 70% identity between the strands is required which will inherently include many situations of non-complementary base pairs separated by complementary base pairs) comprising:

a) preparing at least one heteroduplex polynucleotide, the heteroduplex having first and second strands (see column 2, lines 47-67; since heteroduplex is a double-stranded nucleic acid, it inherently has first and second strands),

b) combining said heteroduplex polynucleotide with enzymes consisting essentially of an effective amount of a mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatched nucleotides, an enzyme or enzymes with 3' to 5' exonuclease activity and an enzyme or enzymes with polymerase activity (see column 17, example 2, where a cellular extract with the MutS mismatch repair enzymes are used, which extract will inherently comprise the naturally present exonucleases and polymerases such as Taq polymerase) and an agent with strand cleavage activity (see column 17, example 2, where the MutH enzyme, part of the MutS mismatch repair system, will also inherently be present and which has strand cleavage activity),

c) allowing sufficient time for the percentage of complementarity to increase wherein one or more sequence variants are made, thereby increasing diversity in a population of polynucleotides (see column 2, lines 47-67, where the enzymes correct the heteroduplex, therefore inherently increasing diversity of a population of polynucleotides and producing at least one variant), and

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (see column 2, lines 47-67 and lines 45-46, which notes "new permutations of mismatches will be generated in the annealing step of each cycle" and see column 19, example 4, where resulting nucleic acids are recovered by cloning).

Regarding claim 69, Vind teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see column 17, example 2, where the cell extract is added).

Regarding claims 70-72, Vind teaches the addition of Taq DNA ligase (see column 17, example where the cell extract, which inherently includes the Taq ligase, is used).

Regarding claim 85, Vind teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see column 2, lines 61-63, where mismatch repair proteins repair mismatches to form homoduplexes).

Regarding claim 87, Vind teaches performance of the method to generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

Regarding claims 88-89, Vind teaches screening for changed properties of the sequence (see column 9, lines 6-12 and column 7, lines 28-38).

Regarding claim 90, Vind teaches 60% homology can be used which would result in three non-complementary base pairs (see column 7, line 43) and that performance of the method will generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections based on the Vind reference

14. Claim 68 rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over Vind (U.S. Patent 6,783,941; cited in the previous office action).

A) Vind teaches addition of all of the ingredients at once, but does not teach adding the ingredients in the particular order claimed in claim 68.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any order of adding ingredients, as MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the first necessary reactant first, the second and the third reactant needed is added last. So in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is prima facie obvious as noted by the MPEP section above.

Rejections based on Arnold et al. reference

15. Claim 68 rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action) as evidenced as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989).

A) Arnold et al. teach addition of all of the ingredients at once, but do not teach adding the ingredients in the particular order claimed in claim 68.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any order of adding ingredients, as MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the first necessary reactant first, the second and the third reactant needed is added last. So in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is prima facie obvious as noted by the MPEP section above.

16. Claims 78 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989), Birkenkamp et al (DNA Research (1995) 2:9-14; cited in the previous office action) and Youil et al. (PNAS USA, vol. 92, pp. 87-91, 1995).

A) Arnold et al. teach the limitations of claim 67, as discussed above, but do not teach the use of the T4 mismatch correction system.

Arnold et al. expressly teach that a variety of different mismatch repair systems can be used (page 16, lines 22-32; page 17, lines 1-23).

B) Birkenkamp et al. teach an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), using the T4 mismatch correction system, including T4 endonuclease VII, T4 DNA ligase and T4 DNA polymerase (see page 11, column 1). They also teach that T4 endonuclease eas used for mapping mutations in heteroduplexes by Youil et al. (page 13, third paragraph).

Youil et al. teach using T4 endonuclease VII to detect mutations in DNA heteroduplexes (Abstract; page 87, second paragraph; page 88, last paragraph; page 89; Fig. 2-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the T4 mismatch correction system in the in vitro mismatch repair method of Arnold et al. since Birkenkamp et al. teach:

"In summary, these observations emphasize further the in vivo role of endonuclease VII as a repair-initiating enzyme that recognizes a wide variety of DNA secondary structures (see page 13, column 2)".

The motivation to do so, provided by Youil et al., would have been, as stated by Youil et al. (page 87, first paragraph):

"The detection of mutations is important, particularly in the diagnosis of inherited diseases. Changes in the DNA sequences of a gene can be harmful and it is important in our understanding of human genetics that we are able to identify and classify these alterations and the phenotypic changes that they induce. Consequently, the need for a reliable method for the detection of mutations in DNA to avoid repetitive sequencing of kilobase lengths of DNA has led to the development of a number of different screening methods that have both positive and negative attributes (see ref. 1 for a review of current mutation detection methods)."

Finally, since Birkenkamp teaches that the T4 system is a known equivalent in the prior art of the other systems detailed by Arnold et al., this falls within the situation described in MPEP 2144.06, which notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

17. Claims 66 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989), Birkenkamp et al (DNA Research (1995) 2:9-14; cited in the previous office action), Youil et al. (PNAS USA, vol. 92, pp. 87-91, 1995) and Oleykowski et al. (Nucl. Acids Res., vol. 26, pp. 4597-4602, 1998; cited in the previous office action).

A) Arnold et al. teach the limitations of claims 66 and 67, as discussed above, but do not teach the use of the T4 mismatch correction system.

Arnold et al. expressly teach that a variety of different mismatch repair systems can be used (page 16, lines 22-32; page 17, lines 1-23).

B) Birkenkamp et al. teach an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), using the T4 mismatch correction system, including T4 endonuclease VII, T4 DNA ligase and T4 DNA polymerase (see page 11, column 1). They also teach that T4 endonuclease eas used for mapping mutations in heteroduplexes by Youil et al. (page 13, third paragraph).

Youil et al. teach using T4 endonuclease VII to detect mutations in DNA heteroduplexes (Abstract; page 87, second paragraph; page 88, last paragraph; page 89; Fig. 2-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the T4 mismatch correction system in the in vitro mismatch repair method of Arnold et al. since Birkenkamp et al. teach:

"In summary, these observations emphasize further the in vivo role of endonuclease VII as a repair-initiating enzyme that recognizes a wide variety of DNA secondary structures (see page 13, column 2)".

The motivation to do so, provided by Youil et al., would have been, as stated by Youil et al. (page 87, first paragraph):

"The detection of mutations is important, particularly in the diagnosis of inherited diseases. Changes in the DNA sequences of a gene can be harmful and it is important in our understanding of human genetics that we are able to identify and classify these alterations and the phenotypic changes that they induce. Consequently, the need for a reliable method for the detection of mutations in DNA to avoid repetitive sequencing of kilobase lengths of DNA has led to the development of a number of different screening methods that have both positive and negative attributes (see ref. 1 for a review of current mutation detection methods)."

Finally, since Birkenkamp et al. teach that the T4 system is a known equivalent in the prior art of the other systems detailed by Arnold et al., this falls within the situation described in MPEP 2144.06, which notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

C) Neither Arnold et al. nor Birkenkamp et al. teach Cel I endonuclease.

D) Oleykowski et al. teach that Cel I is a superior enzyme for mismatch correction (see page 4602, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Cel 1 of Oleykowski et al. in the in vitro mismatch repair method of Arnold et al., Birkenkamp et al. and Youil et al., since Oleykowski et al. state,

"The principle of mismatch recognition by CEL 1 appears to be different from T4 endonuclease VII, which has also been used for enzyme mutation detection. The latter is a resolvase which nicks one strand at the site of a mismatch and then in the other strand across from the DNA nick. Therefore, any nick can produce two corresponding fragments of the two colors. In the case of CEL 1, the two fragments of the two colors represent two totally independent mutation detection events that complement each other to confirm the presence of the mutation. (See page 4602, column 1)."

Oleykowski et al. further note "Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-mismatch DNA sequences. Background non-specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

So, an ordinary practitioner would have two separate motivations to use CEL 1 in the method of Arnold et al., Birkenkamp et al. and Youil et al. in the place of the other mismatch correction systems. First, CEL 1 operates differently than T4 endonuclease VII and only nicks one strand to result in truly independent mutation event detection. Second, CEL I mutation detection is simple, with low background nicking, high signal to noise ratio and uses a stable enzyme, which minimizes wasted effort in assays where the enzyme fails to function.

18. Claim 82 is rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989), Birkenkamp et al (DNA Research (1995) 2:9-14; cited in the previous office action), Youil et al. (PNAS USA, vol. 92, pp.

87-91, 1995) and Oleykowski et al. (Nucl. Acids Res., vol. 26, pp. 4597-4602, 1998; cited in the previous office action).

A) Arnold et al. teach the limitations of claim 67, as discussed above, but do not teach the use of the T4 mismatch correction system.

Arnold et al. expressly teach that a variety of different mismatch repair systems can be used (page 16, lines 22-32; page 17, lines 1-23).

B) Birkenkamp et al. teach an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), using the T4 mismatch correction system, including T4 endonuclease VII, T4 DNA ligase and T4 DNA polymerase (see page 11, column 1). They also teach that T4 endonuclease eas used for mapping mutations in heteroduplexes by Youil et al. (page 13, third paragraph).

Youil et al. teach using T4 endonuclease VII to detect mutations in DNA heteroduplexes (Abstract; page 87, second paragraph; page 88, last paragraph; page 89; Fig. 2-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the T4 mismatch correction system in the in vitro mismatch repair method of Arnold et al. since Birkenkamp et al. teach:

"In summary, these observations emphasize further the in vivo role of endonuclease VII as a repair-initiating enzyme that recognizes a wide variety of DNA secondary structures (see page 13, column 2)".

The motivation to do so, provided by Youil et al., would have been, as stated by Youil et al. (page 87, first paragraph):

"The detection of mutations is important, particularly in the diagnosis of inherited diseases. Changes in the DNA sequences of a gene can be harmful and it is important in our understanding of

human genetics that we are able to identify and classify these alterations and the phenotypic changes that they induce. Consequently, the need for a reliable method for the detection of mutations in DNA to avoid repetitive sequencing of kilobase lengths of DNA has led to the development of a number of different screening methods that have both positive and negative attributes (see ref. 1 for a review of current mutation detection methods)."

Finally, since Birkenkamp et al. teach that the T4 system is a known equivalent in the prior art of the other systems detailed by Arnold et al., this falls within the situation described in MPEP 2144.06, which notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

C) Neither Arnold et al. nor Birkenkamp et al. teach Cel I endonuclease.

D) Oleykowski et al. teach that Cel I is a superior enzyme for mismatch correction (see page 4602, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Cel 1 of Oleykowski et al. in the in vitro mismatch repair method of Arnold et al., Birkenkamp et al. and Youil et al., since Oleykowski et al. state,

"The principle of mismatch recognition by CEL 1 appears to be different from T4 endonuclease VII, which has also been used for enzyme mutation detection. The latter is a resolvase which nicks one strand at the site of a mismatch and then in the other strand across from the DNA nick. Therefore, any nick can produce two corresponding fragments of the two colors. In the case of

CEL 1, the two fragments of the two colors represent two totally independent mutation detection events that complement each other to confirm the presence of the mutation. (See page 4602, column 1)."

Oleykowski et al. further note "Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-mismatch DNA sequences. Background non-specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

So, an ordinary practitioner would have two separate motivations to use CEL 1 in the method of Arnold et al., Birkenkamp et al. and Youil et al. in the place of the other mismatch correction systems. First, CEL 1 operates differently than T4 endonuclease VII and only nicks one strand to result in truly independent mutation event detection. Second, CEL I mutation detection is simple, with low background nicking, high signal to noise ratio and uses a stable enzyme, which minimizes wasted effort in assays where the enzyme fails to function.

E) None of the references cited above teach T7 DNA polymerase.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to substitute the T4 DNA polymerase in the method of Arnold et al., Birkenkamp et al., Youil et al. and Oleykowski et al. by another DNA polymerase, such the T7 DNA polymerase, since both were recognized in the art as equivalent in terms of DNA synthesis. This falls within the situation described in MPEP 2144.06, which notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on

applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

19. Claims 91, 93-96 and 98-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989) and Oleykowski et al. (Nucl. Acids Res., vol. 26, pp. 4597-4602, 1998; cited in the previous office action).

A) Regarding claim 91, Arnold et al teach an in vitro method of making linear sequence variants comprising:

a) preparing at least one heteroduplex polynucleotide, the heteroduplex having first and second strands (page 2, lines 32, 33; page 3, lines 1-5; lines 11-33; page 4, lines 1-9; since heteroduplex is a double-stranded nucleic acid, it inherently has first and second strands),

b) combining said heteroduplex polynucleotide with enzymes consisting essentially of an effective amount of a mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatched nucleotides, an enzyme or enzymes with 3' to 5' exonuclease activity and an enzyme or enzymes with polymerase activity (Arnold et al. teach mixing the heteroduplexes with either intact cells or cell extracts containing mismatch-endonuclease activity, an enzyme with 3' to 5' exonuclease activity and enzyme with polymerase activity (page 3, lines 2-5;10; page 4, lines 24-26; page 9, lines 12-33; page 16, lines 22-33; page 17, lines 1-33; page 18, lines 1-3). As evidenced by Lahue et al., E. coli contains a DNA polymerase and a ligase which participate in the repair reactions (page 161, second paragraph), therefore by teaching E. coli cells Arnold et al. inherently teach a polymerase. Further, since the E. coli cells contain a repair system which contain cellular

repair system with mismatch endonuclease, Arnold et al. inherently teach mismatch endonuclease. Finally, E. coli cells contain enzymes with 3' to 5' exonuclease activity, for example DNA polymerase PolI.),

c) allowing sufficient time for the percentage of complementarity to increase wherein one or more sequence variants are made, thereby increasing diversity in a population of polynucleotides (Arnold et al. teach allowing sufficient time to proceed with a repair mechanism and produce variant nucleotides (page 18, lines 6-8), therefore inherently increasing diversity of a population of polynucleotides and producing at least one variant), and

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (page 3, lines 11-25), where resulting nucleic acids are inherently separated and recovered by cloning).

Regarding claim 93, Arnold et al teach concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (page 9, lines 21-22, where the cell extract is added).

Regarding claims 94-96, Arnold et al teach the addition of E. coli DNA ligase in cell extracts (page 9, lines 21-22; page 17, line 33; where the cell extract from E. coli is added, which inherently includes E. coli ligase).

Regarding claims 98 and 99, Arnold et al teach the addition of E. coli DNA polymerase I in cell extracts (page 9, lines 21-22, page 17, line 33; where the cell extract from E. coli is added which inherently includes E. coli DNA polymerase I).

Regarding claim 101, Arnold et al teach that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (page 23, lines 10-32; page 24, lines 1-8).

Regarding claim 102, Arnold et al teach performance of the method to generate a library of different nucleotide sequences (page 23, lines 10-32; page 24, lines 1-8, for example).

Regarding claims 103and 104, Arnold et al teach screening for changed properties of the sequence (page 3, lines 4, 5; page 4, lines 27-30; page 6, lines 30-33; page 7, lines 1-5; page 9, lines 30-33; page 18, lines 30; page 19, lines 1-9).

Regarding claim 105, Arnold et al teach 56% homology can be used which would result in at least three non-complementary base pairs that performance of the method will generate at least four sequence variants (page 22, 23, page 24, lines 1-8, for example).

B) Arnold et al. do not teach Cel I endonuclease.

C) Regarding claims 91 and 100, Oleykowski et al. teach that Cel I is a superior enzyme for mismatch correction (see page 4602, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Cel 1 of Oleykowski et al. in the in vitro mismatch repair method of Arnold et al., since Oleykowski et al. state,

"The principle of mismatch recognition by CEL 1 appears to be different from T4 endonuclease VII, which has also been used for enzyme mutation detection. The latter is a resolvase which nicks one strand at the site of a mismatch and then in the other strand across from the DNA nick. Therefore, any nick can produce two corresponding fragments of the two colors. In the case of CEL 1, the two fragments of the two colors represent two totally independent mutation detection events that complement each other to confirm the presence of the mutation. (See page 4602, column 1)."

Oleykowski et al. further note "Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-mismatch DNA sequences. Background non-

specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

So, an ordinary practitioner would have two separate motivations to use CEL 1 in the method of Arnold et al. in the place of the other mismatch correction systems. First, CEL 1 operates differently than T4 endonuclease VII and only nicks one strand to result in truly independent mutation event detection. Second, CEL I mutation detection is simple, with low background nicking, high signal to noise ratio and uses a stable enzyme, which minimizes wasted effort in assays where the enzyme fails to function.

20. Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989) and Oleykowski et al. (Nucl. Acids Res., vol. 26, pp. 4597-4602, 1998; cited in the previous office action).

A) Arnold et al. teach addition of all of the ingredients at once, but do not teach adding the ingredients in the particular order claimed in claim 92.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any order of adding ingredients, as MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the first necessary reactant first, the second and the third reactant needed is added last. So in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is prima facie obvious as noted by the MPEP section above.

21. Claim 97 is rejected under 35 U.S.C. 103(a) as being unpatentable over over Arnold et al. (WO 99/29902; cited in the IDS and in the previous office action), as evidenced by Lahue et al. (Science, vol. 245, pp. 160-164, 1989) and Oleykowski et al. (Nucl. Acids Res., vol. 26, pp. 4597-4602, 1998; cited in the previous office action).

A) None of the references cited above teach T7 DNA polymerase.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to substitute the E. coli DNA polymerase in the method of Arnold et al., another DNA polymerase, such the T4 DNA polymerase, since both were recognized in the art as equivalent in terms of DNA synthesis. This falls within the situation described in MPEP 2144.06, which notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with

this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 67, 70, 71, 78, 79, 88 and 89 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6, 7 and 10 of U.S. Patent No. 7,056,740. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 6, 7 and 10 of the '740 patent are species of claims 67, 70, 71, 78, 79, 88 and 89.

Specifically, claim 1 of the '740 patent is drawn to a method of obtaining a peptide sequence of desired functional property, the method comprising:

a) preparing at least one heteroduplex polynucleotide sequence wherein said heteroduplex polynucleotide sequence has at least two non-complementary nucleotide base pairs;

b) mixing copies of the heteroduplex polynucleotide sequence with an effective amount of RES I or a combination of mismatch endonucleases including RES I, a proofreading enzyme, dNTPs, and a ligase enzyme;

c) allowing sufficient time for non-complementary nucleotide base pairs to be converted to complementary base pairs, wherein a population of polynucleotide sequence variants result;

d) expressing polynucleotide sequence variants; and

e) screening or selecting variants for the desired functional property, wherein at least one of the polynucleotide sequence variants selected encode peptide sequence variants that have superior biological activity compared to the peptides encoded by the polynucleotide sequences used to form the heteroduplex.

Claim 7 is a slight variation of claim 1. Therefore, claims 1 and 7 of the '740 patent are species of claims 67, 70, 71, 88 and 89 of the instant application, therefore they anticipate these

claims. Further, claims 6 and 10 of the '740 patent anticipate claims 78 and 79 of the instant application.

24. Claims 67-72, 78, 79, 88-89, 91-98, 100 and 102-104 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4 and 6 of U.S. Patent No. 7,217,514. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 4 and 6 of the '514 patent are species of claims 67-72, 78, 79, 88-89, 91-98, 100 and 102-104.

Specifically, claim 1 of the '514 patent is drawn to an in vitro method of making circular sequence variants from one or more circular heteroduplex polynucleotides wherein said heteroduplex polynucleotides have at least two non-complementary nucleotide base pairs separated by complementary nucleotide base pairs, said method comprising:

a) preparing the one or more circular heteroduplex polynucleotides;

b) sequentially or concurrently combining said circular heteroduplex polynueleotides with purified enzymes wherein the enzymes consist essentially of an effective amount of a mismatch recognizing and mismatch directed endonuclease CEL I, T4 DNA polymerase, and E. coli DNA ligase;

c) allowing sufficient time for the percentage of complementarity and diversity in a population of polynucleotides to increase such that one or more circular sequence variants are made which are different from the circular heteroduplex polynueleotides, and which contain a partial sequence matching each polynucleotide in the circular heteroduplex polynueleotides;

d) separating said sequence variants from the polynucleotides which make up the circular heteroduplex polynucleotide; and

e) recovering said circular sequence variants, wherein at least one circular sequence variant has a different desired functional property from the polynucleotides in said one or more circular heteroduplex polynucleotides.

Therefore, claim 1 of the '514 patent anticipates claims 67-72, 78, 79, 89, 91-98, 100 and 104 of the instant application. Claims 4 and 6 of the '514 patent anticipate instant claims 87, 88, 102 and 103.

25. Claims 67, 70, 87, 88, 89, 91, 94, 100 and 102-104 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 7,235,386. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 6 of the '386 patent are species of claims 67, 70, 87, 88, 89, 91, 94, 100 and 102-104.

Specifically, claim 1 of the '386 patent is drawn to a method of obtaining a polynucleotide variant comprising the steps of:

a) preparing at least one first heteroduplex polynucleotide from partially complementary polynucleotide strands, said first heteroduplex polynucleotide having at least two mismatched base pairs;

b) combining said heteroduplex polynucleotide with an effective amount of purified enzymes, wherein the enzymes comprise a polymerase, a ligase and a mismatch directed endonuclease selected from the group consisting of CEL I, T4 endonuclease VII, T7 endonuclease I, and SP nuclease;

c) allowing sufficient time for the percentage of complementarity between the strands of said heteroduplex polynucleotide to increase so that variants are made that have sequences different from any of said partially complementary polynucleotide strands;

d) screening or selecting for a population of variants having a desired functional property from the variants; denaturing at least one of said population of variants to obtain single strand polynucleotides;

f) annealing said single strand polynucleotides to form at least one second heteroduplex polynucleotide, wherein at least one strand in the second heteroduplex is a variant and said second heteroduplex polynucleotide has at least two mismatched base pairs;

g) combining said second heteroduplex polynucleotide with an effective amount of purified enzymes, wherein the enzymes comprise a polymerase, a ligase, and a mismatch directed endonuclease selected from the group consisting of CEL I, T4 endonuclease VII, T7 endonuclease I, and SP nuclease;

h) allowing sufficient time for the percentage of complementarity between the strands of the heteroduplex polynucleotide to increase so that additional variants are made that have sequences different from any of the partially complementary polynucleotide strands and different from any of the variants made in step c), and being different from either strand in the second heteroduplex;

i) screening or selecting for a population of additional variants having a desired functional property from the additional variants different from any of the variants made in step c) and different from any of said partially complementary polynucleotide strands; and

j) recovering an additional variant from the population of additional variants.

Therefore, claim 1 of the '386 patent anticipates claims 67, 70, 87, 88, 91, 94, 100, 102 and 103 of the instant application. Further, claim 6 of the '386 patent anticipates claims 89 and 104.

26. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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2/15/08